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ATTORNEY'S DOCKET NUMBER: GIN-6730CPUS

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C.371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/019788

INTERNATIONAL APPLICATION	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/03942	16 June 2000 (16.06.00)	08 July 1999 (08.07.99)

TITLE OF INVENTION

HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

APPLICANT(S) FOR DO/EO/US

Seishi KATO, *et al.*

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C.371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(unexecuted) (4 Sheets);**
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98;
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
13. ☐ A FIRST preliminary amendment;
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: **PCT International Published Application (WO 01/04297 A2) (without International Search Report attached) (150 sheets); Corrected Version of Cover Sheet of PCT International Application (WO 01/04297 A3) (with International Search Report attached) (7 sheets); The International Preliminary Examination Report (7 sheets); Check for $1300 based on large entity status; Certificate of First Class Mailing (1 sheet); and Return Postcard.**

JC13 Rec'd PCT/PTC 04 JAN 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NO
10/019788	PCT/JP00/03942	GIN-6730CPUS

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) .(a/o November 1, 2000):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....**$1040**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.455(a)(2)) paid to USPTO **$740**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4).....**$710**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....**$100**

CALCULATIONS PTO USE ONLY	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$130.00	
CLAIMS	**NUMBER FILED**	**NUMBER EXTRA**	**RATE**		
Total claims	**12**-20 =	**0**	X **$18.00**	$	
Independent claims	**2**-3 =	**0**	X **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **280.00**	$280.00	
TOTAL OF ABOVE CALCULATIONS =				$1300.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$	
SUBTOTAL =				$1300.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$1300.00	
				Amount to be: refunded	$
				charged	

a. ☒ Check in the amount of $ 1300.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **12-0080**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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37,320
REGISTRATION NUMBER

DESCRIPTION

Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic cells expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like are currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the

whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03394.

Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03395.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10685.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10686.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10689.

Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10690.

Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10694.

Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10696.

Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10697.

Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10699.

SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins

having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10. Moreover, the present invention provides a DNA encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in

vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, incorporation of the translated region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as *Escherichia coli* etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for *Escherichia coli* are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced

as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or

solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells

affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)$^+$ RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any

portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20 or the base sequences represented by SEQ ID NOS: 21 to 30. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

SEQ ID NO	HP number	Cell	Number of bases	Number of amino acid residues
1, 11, 21	HP03394	Umbilical cord blood	2007	339
2, 12, 22	HP03395	Thymus	2264	487
3, 13, 23	HP10685	Umbilical cord blood	1907	262
4, 14, 24	HP10686	PMA-U937	1727	166
5, 15, 25	HP10689	Umbilical cord blood	2150	416
6, 16, 26	HP10690	Umbilical cord blood	1986	117
7, 17, 27	HP10694	Umbilical cord blood	2170	324
8, 18, 28	HP10696	Umbilical cord blood	1738	137
9, 19, 29	HP10697	Thymus	1930	311
10, 20, 30	HP10699	Umbilical cord blood	1892	543

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30 shall come within the scope of the present invention.

Similarly, any protein in which one or plural

amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20 or in the base sequences represented by SEQ ID NOS: 21 to 30. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat,

a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to

map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines

including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a.

Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6- Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark,S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect

APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically,

infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down

regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign

by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used

include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief

from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the

present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected

tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the

activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental

Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al.,

Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-

mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those

described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the

present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or

sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and

traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent

Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the

ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other

trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach,

W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al.,

Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current

Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)),

ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing,

infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an

antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA libraries constructed from phorbol ester-stimulated histiocytic lymphoma cell line U937 (ATCC CRL 1593) mRNA, human thymus mRNA (Clontech) and human umbilical

cord blood mRNA were used as cDNA libraries.

Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of T_NT rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached

to the kit), 2 µl of an amino acid mixture (without methionine), 2 µl of [^{35}S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried out by adding 2.5 µl of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 µl of the reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100 µg/ml of ampicillin, the helper phage M13KO7 (50 µl) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO_2 in the

Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10^5 COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO_2. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAM™ (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO_2. After the medium was exchanged for a medium containing [^{35}S]cysteine or [^{35}S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na_2HPO_4, 2 mM KH_2PO_4, pH 7.2) to a concentration of 2 µg/µl. 25 µl each (a total of 50 µl) of the thus-prepared plasmid solution in

PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN_3 was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed by immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a cell lysate or a secreted product.

(5) Clone Examples

<HP03394> (SEQ ID NOS: 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03394 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 45-bp 5'-untranslated region, a 1020-bp ORF, and a 942-bp 3'-untranslated region. The ORF encodes a protein consisting of 339 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product

of 42 kDa that was somewhat larger than the molecular weight of 36,856 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamine at position 21.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human monocyte inhibitory receptor (Accession No. AAB68665). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human monocyte inhibitory receptor (MI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.2% in the N-terminal region of 236 amino acid residues.

Table 2

```
HP MSPSPTALFCLGLCLG-RVPAQSGPLPKPSLQALPSSLVPLEKPVTLRCQGPPGVDLYRL
   * *. ***.****.** *.. *.******.* * *.*... ...**..***. ..  ***
MI MIPTFTALLCLGLSLGPRTHMQAGPLPKPTLWAEPGSVISWGNSVTIWCQGTLEAREYRL
HP EK-LSSSRYQDQAVL-------F-IPAMKRSLAGRYRCSYQNGSLWSLPSDQLELVATGV
   .* *..... *. *       * **.*. . ****** *..   ** ***.**** **.
```

```
MI DKEESPAPWDRQNPLEPKNKARFSIPSMTEDYAGRYRCYYRSPVGWSQPSDPLELVMTGA
HP FAKPSLSAQPGPAVSSGGDVTLQCQTRYGFDQFALYKEGDPAPYKN--PER---WYRASF
   ..**.*** *.* *.** .*** **.*  .* * * ** .. *  .  .*.    ..*.*
MI YSKPTLSALPSPLVTSGKSVTLLCQSRSPMDTFLLIKERAAHPLLHLRSEHGAQQHQAEF
HP PIITVTAAHSGTYRCYSFSSRDPYLWSAPSDPLELVVTGTSVTPSRLPTEPPSSVAEFSE
   *. .**..*.*****.*  . ..** * *******.*.*.  .*.. ** . *..*
MI PMSPVTSVHGGTYRCFSSHGFSHYLLSHPSDPLELIVSGSLEGPRPSPTRSVSTAAGPED
HP ATAELTVSFTNEVFTTETSRSITASPKESDSPAGPARQYYTKGNLVRICLGAVILIILAG

MI QPLMPTGSVPHSGLRRHWEVLIGVLVVSILLLSLLLFLLLQHWRQGKHRTLAQRQADFQR
HP FLAEDWHSRRKRLRHRGRAVQRPLPPLPPLPLTRKSHGGQDGGRQDVHSRGLCS

MI PPGAAEPEPKDGGLQRRSSPAADVQGENFCAAVKNTQPEDGVEMDTRQSPHDEDPQAVTY
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA308708) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03395> (SEQ ID NOS: 2, 12, and 22)

Determination of the whole base sequence of the cDNA insert of clone HP03395 obtained from cDNA library of

human thymus revealed the structure consisting of a 84-bp 5'-untranslated region, a 1464-bp ORF, and a 716-bp 3'-untranslated region. The ORF encodes a protein consisting of 487 amino acid residues and there existed at least six putative transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the present protein had additional 106 amino acid residues at the N-terminus as compared with human putative protein C3f (Accession No. AAC36007).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA182534) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10685> (SEQ ID NOS: 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10685 obtained from cDNA library of human umbilical cord blood revealed the structure consisting

of a 34-bp 5'-untranslated region, a 789-bp ORF, and a 1084-bp 3'-untranslated region. The ORF encodes a protein consisting of 262 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminnus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,330 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 29 kDa. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Thr-Ser at position 182). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 28.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA448745) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10686> (SEQ ID NOS: 4, 14, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP10686 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 19-bp 5'-untranslated region, a 501-bp ORF, and a 1207-bp 3'-untranslated region. The ORF encodes a protein consisting of 166 amino acid residues and there existed three putative transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI275139) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10689> (SEQ ID NOS: 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP10689 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 31-bp 5'-untranslated region, a 1251-bp ORF, and a 868-bp 3'-untranslated region. The ORF encodes a protein consisting of 416 amino acid residues and there existed one putative transmembrane domain. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 44 kDa that was somewhat smaller than the molecular weight of 46,451 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 48 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Gly-Thr at position 160 and Asn-Met-Ser at position 196).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Arabidopsis thaliana putative strictosidine synthase (Accession No. AAC27642). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Arabidopsis thaliana putative strictosidine synthase (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.4% in the entire region other than the N-terminal region.

Table 3

```
HP MSEADGLRQRRPLRPQVVTDDDGQAPEAKDGSSFSGRVFRVTFLMLAVSLTVPLLGAMML

AT                                                        MMKLLLVVAT
HP LESPIDPQPLSFKEPPLLLGVLHPNTKLRQAERLFENQLVGPES--IAHIGDVMFTGTAD
                                                  .****  ..  .**  .** .*
AT SVALIFSVTDLSGEGPKHGGESMLTVQIPDFRLIPTTGALGPESFVFDFFGDGPYTGLSD
HP GRVVK-LENGEI------ETIARFG-SGPCKTRDDEPVCGRPLGIR-AGPNGTLFVADAY
   **.** *.*..        .* ** * .** .  .  .*.*******.   .  ..*.*..****
AT GRIVKWLANESRWIDFAVTTSAREGCEGPHEHQRTEHVCGRPLGLAFDKSTGDLYIADAY
HP KGLFEVNPWKREVKLLLSSETPIEGKNMSFVNDLTVTQDGRKIYFTDSSSKWQRRDYLLL
   .**..*.*    ..  .*..*    .....*.*.*.... .   .******* .***.*.
AT MGLLKVGPTGGVANQVLPRE---LNEALRFTNSLDINPRTGVVYFTDSSSVYQRRNYIGA
HP VMEGTDDGRLLEYDTVTREVKVLLDQLRFPNGVQLSPAEDFVLVAETTMARIRR-----V
   .*.*...***..**.  *..*..**..* * ***.**...*..**.**.* ** *     .
AT MMSGDKTGRLMKYDN-TKQVTTLLSNLAFVNGVALSQNGDYLLVVETAMCRILRYWLNET
HP YVSGLMKGGADLFVENMPGFPDNIRPSSSGGYWVGMSTIRPNPGFSMLDFLSERPWIKRM
    *..  ... ..*.*..*******..*..**.***..*       .. .*  ...*. *
AT SVKSQSHDNYEIFAEGLPGFPDNIKRSPRGGFWVGLNT----KHSKLTKFAMSNAWLGRA
HP IFKLFSQ-ETVMKFVPRY---SLVLELS-DSGAFRRSLHDPDGLVATYISEVHEHDGHLY
    . *  .  .* .  .** : .... ** ***..   ... ..   . ****.*.** *.
AT ALGLPVDWMKVHSVWARYNGNGMAVRLSEDSGVILEVFEGKNENKWISISEVEEKDGTLW
HP LGSFRSPFLCRLSLQAV
   .** ..**
AT VGSVNTPFAGMYKI
```

[redacted]

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI750995) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10690> (SEQ ID NOS: 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP10690 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 27-bp 5'-untranslated region, a 354-bp ORF, and a 1605-bp 3'-untranslated region. The ORF encodes a protein consisting of 117 amino acid residues and there existed one putative secretory signal at the N-terminus. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 15 kDa that was somewhat larger than the molecular weight of 12,647 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 14 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts

from aspartic acid at position 23.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA215334) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10694> (SEQ ID NOS: 7, 17, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10694 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 240-bp 5'-untranslated region, a 975-bp ORF, and a 955-bp 3'-untranslated region. The ORF encodes a protein consisting of 324 amino acid residues and there existed at least seven putative transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI245647) among ESTs. However, since they are partial sequences, it can not be judged whether or not they

encode the same protein as the protein of the present invention.

<HP10696> (SEQ ID NOS: 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10696 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 94-bp 5'-untranslated region, a 414-bp ORF, and a 1230-bp 3'-untranslated region. The ORF encodes a protein consisting of 137 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 20 kDa that was somewhat larger than the molecular weight of 14,492 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D31289) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10697> (SEQ ID NOS: 9, 19, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10697 obtained from cDNA library of

human thymus revealed the structure consisting of a 81-bp 5'-untranslated region, a 936-bp ORF, and a 913-bp 3'-untranslated region. The ORF encodes a protein consisting of 311 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 37 kDa that was somewhat larger than the molecular weight of 33,901 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 51 kDa. In addition, there exist in the amino acid sequence of this protein six sites at which N-glycosylation may occur (Asn-Val-Thr at position 49, Asn-Leu-Thr at position 91, Asn-Thr-Ser at position 108, Asn-Phe-Ser at position 128, Asn-Leu-Thr at position 135 and Asn-Ile-Thr at position 190). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from phenylalanine at position 33.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W46202) among ESTs. However, since they are

partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10699> (SEQ ID NOS: 10, 20, and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10699 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 4-bp 5'-untranslated region, a 1632-bp ORF, and a 256-bp 3'-untranslated region. The ORF encodes a protein consisting of 543 amino acid residues and there existed at least six putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein C15H9.5 (Accession No. AAB52667). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein C15H9.5 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the

present invention, respectively. The both proteins shared a homology of 33.8% in the region of 461 amino acid residues other than the N-terminal and C-terminal regions.

Table 4

```
HP MAVSERRGLGRGSPAEWGQRLLLVLLLGGCSGRIHRLALTGEKRADIQLNSFGFYTNGSL

CE       MIGNGNVIQADSRRNIIISDFSYGTNGTLSIAINNFTVPEKIKDSVDSTENADKL
HP EVELSVLRLGLREAEEKSLLVGFSLSRVRSGRVRSYSTRDFQDCPLQKNSSSFLVLFLIN
                          ..***** . *. .*. ...  . *.**... .. ..*...
CE VSTTICPQVLTCTYRFLQGVIGFSLS-LGSSITRGVGSNP-HVCQLQQTDQGYDAIFFFA
HP TKDLQVQVRKYGEQKTLFI-FPGLLPEAPSKPGL--PKPQATVPRKVDGGGTSAAS-KPK
   .   . *.* * .  . .* . *  .* ... ..  ***..  * . .*  .  .  .
CE DLP-NKQLRVYRSGIGRYIQICGTAHECQNTDAIRTPKPEELQPESSSGPVEQRGWFRNL
HP STPAVIQGPSGKDKDLVLGLSHLNNSYNFSFHVVIGSQAE-EGQYSLNFHNC-NNSVPG-
    .. . .*..  . *  . * ...*. .** .. *  ...  *** . **** * ...*
CE FGRFLNPGAPQIAYDNYIPL-QVQNENQFSTNMSIRFDGKIVGQYVFMFHNCYNYRAHGY
HP -KEHPFDITVMIREKNPDGFLSAAEMPLFKLYMVMSACFLAAGIFWVSILCR-NTYSVFK
     .  . *.** . *.* ...** .*..  ..*. **  ... ...*  .*** *. ....
CE SDRVAVDLTVDLVERNKHSYLSLQEIAKPEIYLYMSILYFGLAVYWSHLLCRSNSENIYR
HP IHWLMAALAFTKSISLLFHSINYYFINSQGHPIEGLAVMYYIAHLLKGALLFITIALIGS
   .* .**.*.* *..*..**..****... * . *  **.***.***** *** *.  ***.
CE VHKFMAVLVFLKALSVFFHGLNYYFLSKYGMQKEIWAVLYYITHLLKGLLLFGTLILIGT
HP GWAFIKYVLSDKEKKVFGIVIPMQVLANVAYIIIESREEGASDYVLWKEILFLVDLICCG
```

```
   *..***  *.*...*** .*.*.**..*.  **....* *. ..  * ... ..**.**.
CE GYTFIKQFLTDRDRKVFMFVLPIQVIDNIILIILNESEIGTQNHETWLKLFVILDLFCCA
HP AILFPVVWSIRHLQDASGTDGKVAVNLAKLKLFRHYYVMVICYVYFTRIIA-ILLQVAV-
    . **.****.** ....****.*.**.**.***..*..*. *.* **... ***...*
CE LVAFPIVWSIQHLVEGATTDGKAAANLEKLRLFRQFYILVVVYIYCTRFFGFILLPAPVG
HP ------------------PFQWQWLYQLLVEGSTLAFFVLTGYKFQPTGNNPYLQLPQE
                       * . **     **  *.***...****.*.... ** *  .
CE KVLKPHFCGAKIPNITHLMPVNLQWTIVAAVEMVTFAFFIIVGYKFRPANSHNYLLLNSD
HP DEEDVQMEQVMTDSGFREGLSKVNKTASGRELL

CE FDSYDVETSPKEDRKDKENNEQEIDEQFLTKAYSDANVSRRLVSDESSNNQTDYPHQKLL
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R11941) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs and eukaryotic cells

expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents which act to control the proliferation and/or the differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes are introduced to express these proteins can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated

expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed

herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with

altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize

overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with

sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 5

Stringency Condition	Poly-nucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T_B*; 1×SSC	T_B*; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T_D*; 1×SSC	T_D*; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T_F*; 1×SSC	T_F*; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T_H*; 4×SSC	T_H*; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T_J*; 4×SSC	T_J*; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T_L*; 2×SSC	T_L*; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T_N*; 6×SSC	T_N*; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T_P*; 6×SSC	T_P*; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T_R*; 4×SSC	T_R*; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*$T_B - T_R$: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(°C)=2(\#of\ A + T\ bases) + 4(\#\ of\ G + C\ bases)$. For hybrids between 18 and 49 base pairs in length, $T_m(°C)=81.5 + 16.6(\log_{10}[Na^+]) + 0.41\ (\%G+C) - (600/N)$, where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10.

2. An isolated DNA encoding the protein according to Claim 1.

3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 20.

4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30.

5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.

6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.

7. An antibody directed to the protein according to Claim 1.

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WO 01/04297 A2

(51) International Patent Classification[7]: C12N 15/12, C07K 14/705, 14/47, 16/18, 16/28

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(25) Filing Language: English

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(30) Priority Data:
11/194359 8 July 1999 (08 07 1999) JP

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KATO, Seishi** [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP) **KIMURA, Tomoko** [JP/JP]; 715, 2-9-1, Kohoku, Tsuchiura-shi, Ibaraki 300-0032 (JP)

(74) Agents: **AOYAMA, Tamotsu** et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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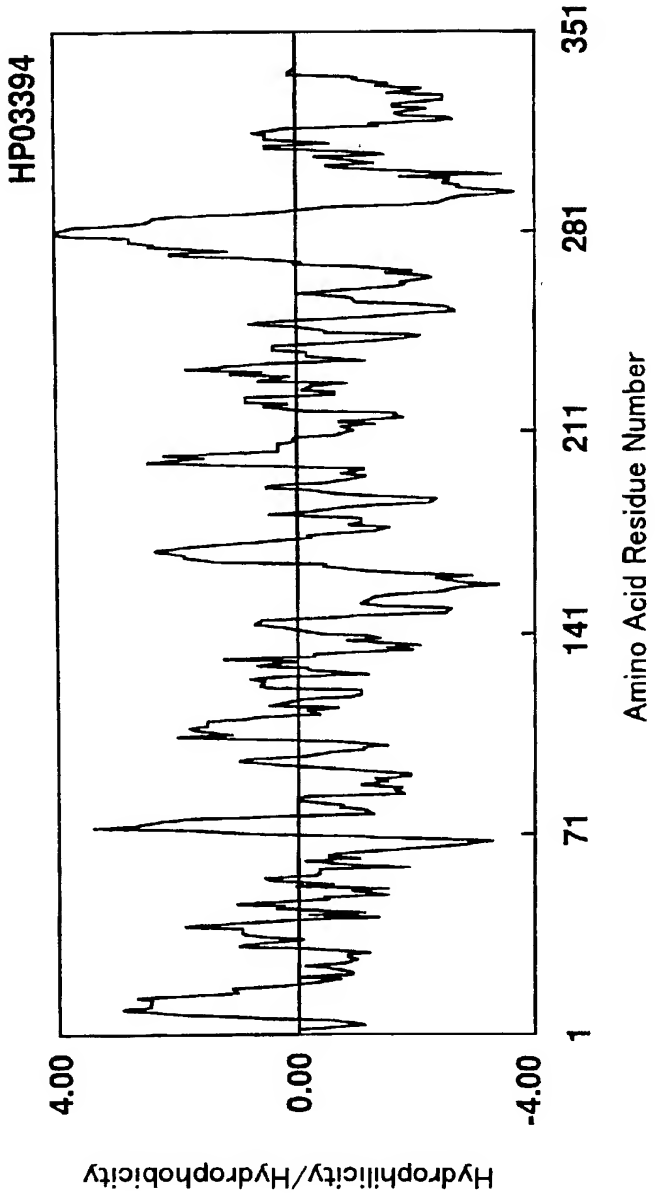
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.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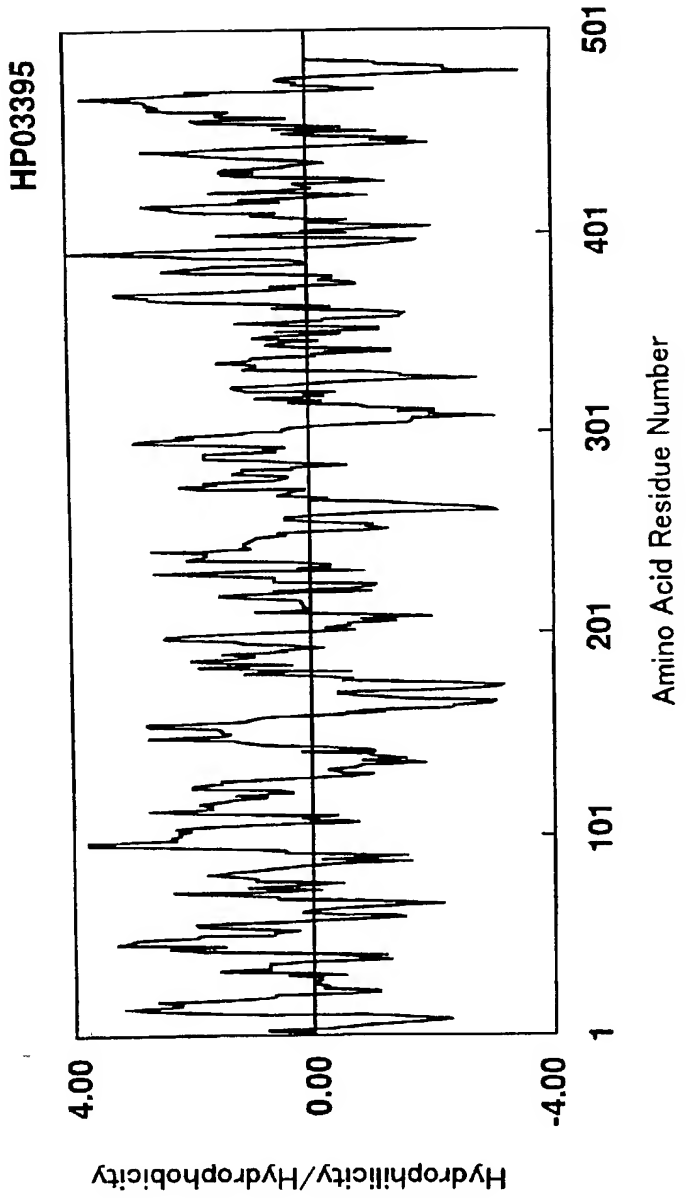
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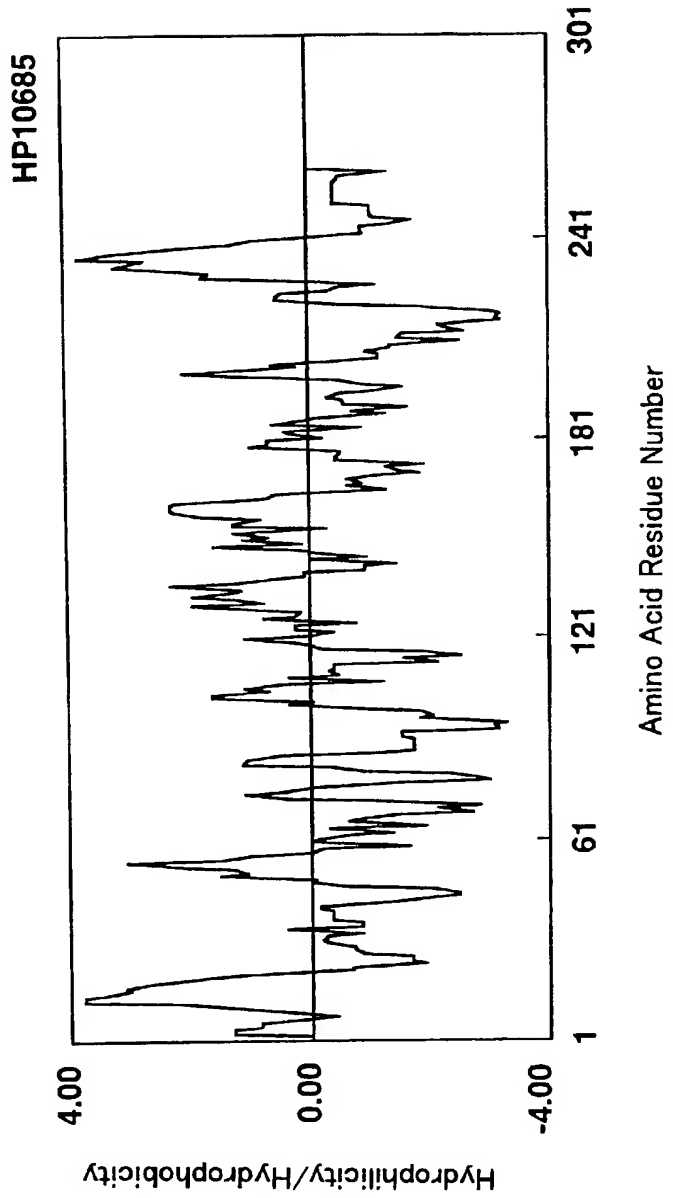
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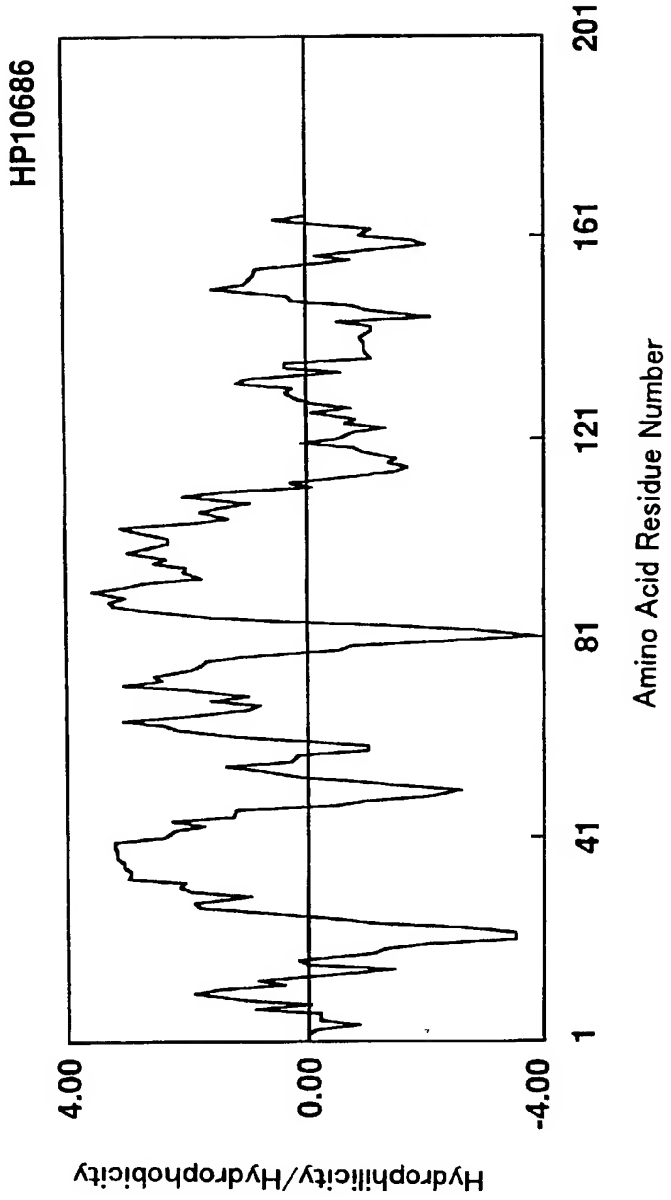
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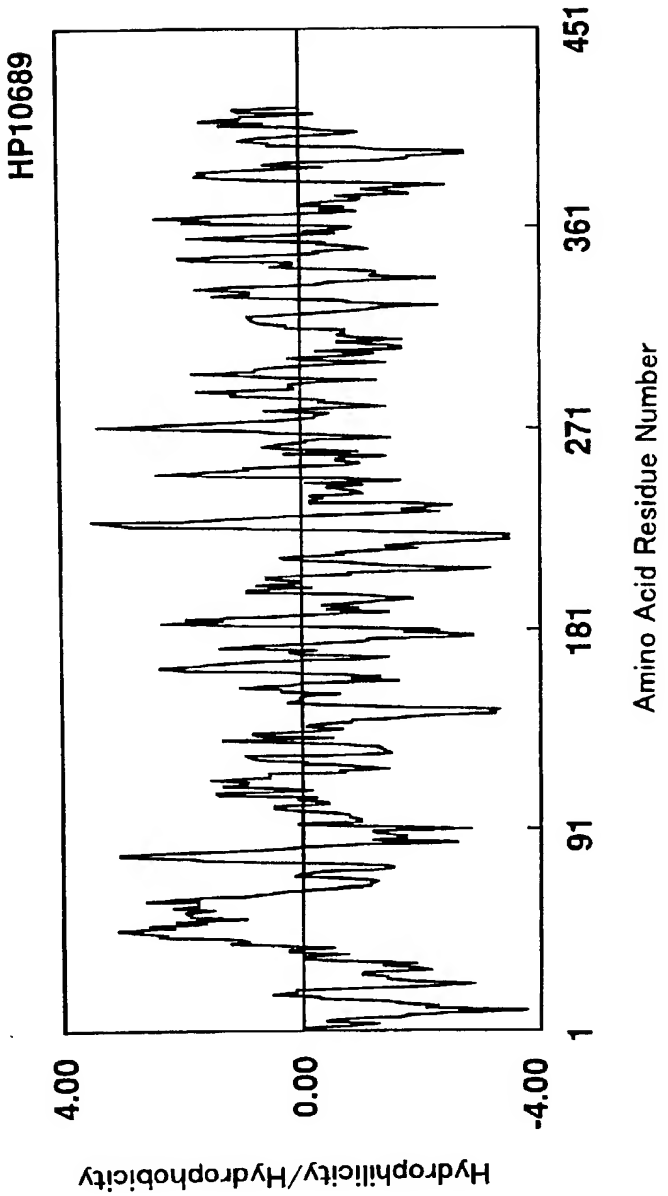
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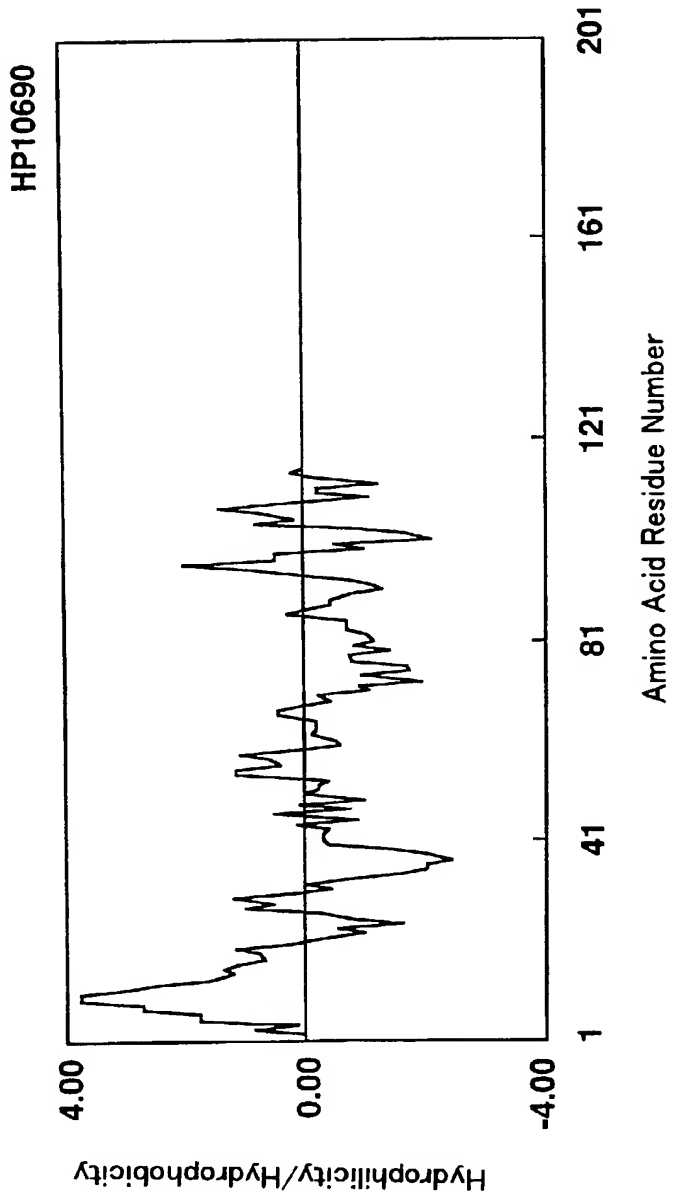
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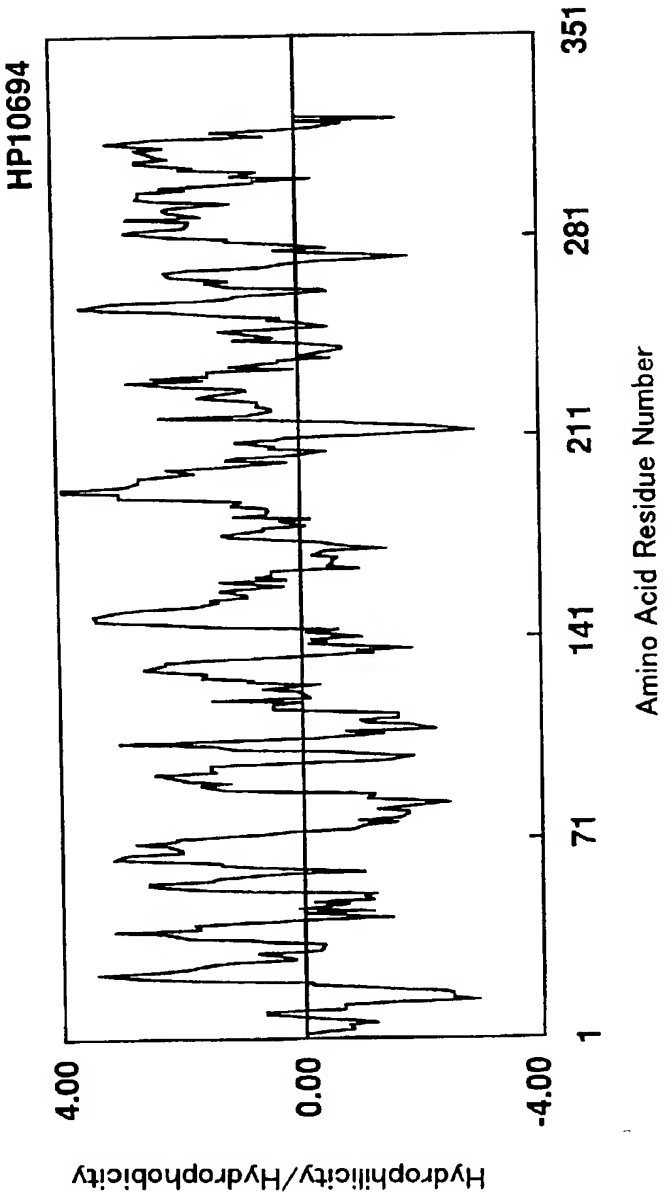
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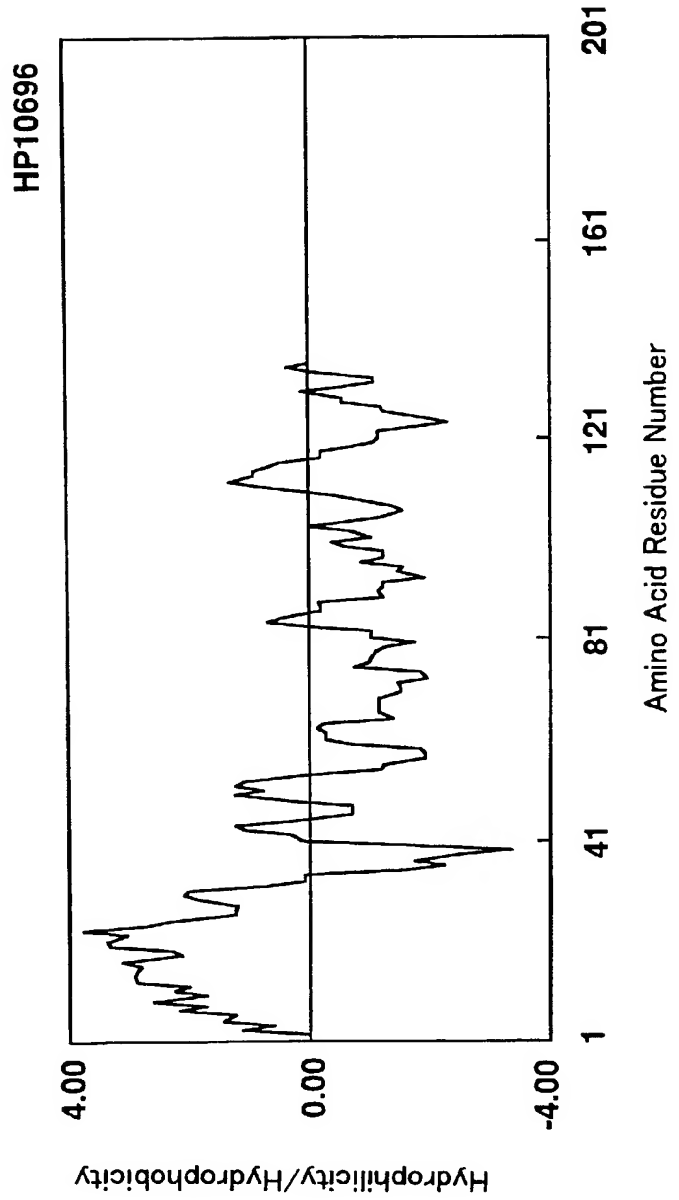
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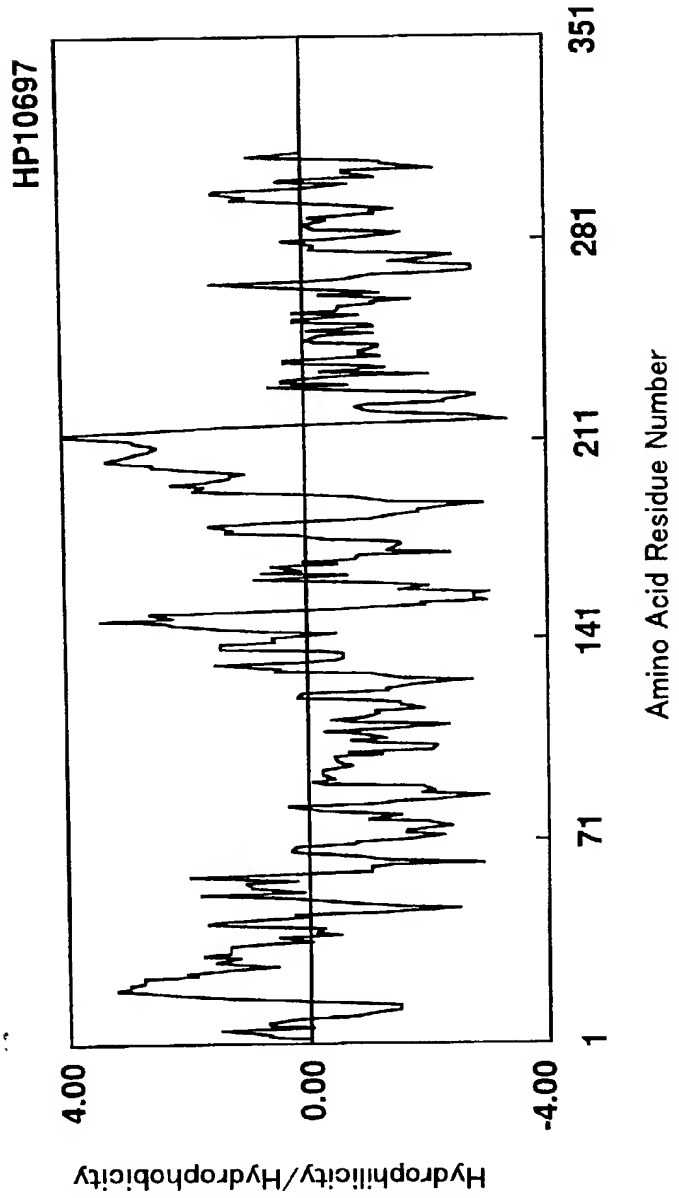
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Fig.9

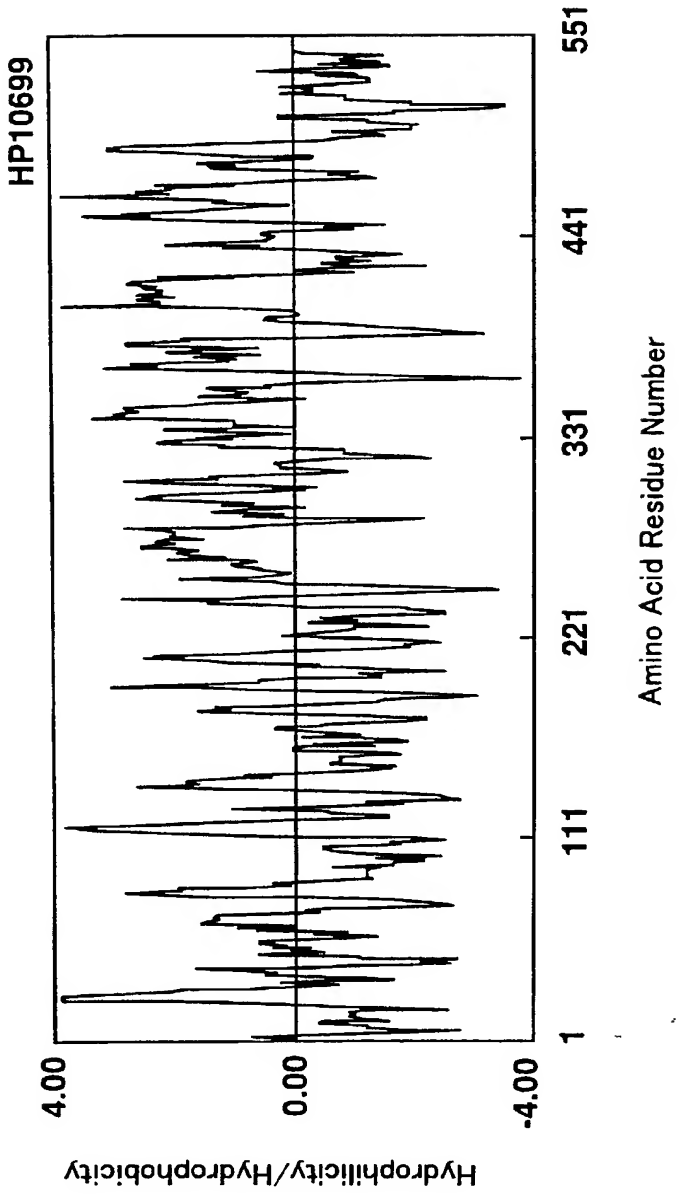
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Fig.10

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Leu Gln Val Pro Gly Asn Thr Leu Pro Ser Pro Pro Pro Ala Ala Ala

165 170 175

Ala Ser Pro Met Pro Leu His Ile Thr Pro Leu Gly Leu Leu Leu Leu

180 185 190

Ile Leu Tyr Cys Leu Ile Ser Gly Leu Ser Ser Val Tyr Thr Glu Leu

195 200 205

Leu Met Lys Arg Gln Arg Leu Pro Leu Ala Leu Gln Asn Leu Phe Leu

210 215 220

Tyr Thr Phe Gly Val Leu Leu Asn Leu Gly Leu His Ala Gly Gly Gly

225 230 235 240

Ser Gly Pro Gly Leu Leu Glu Gly Phe Ser Gly Trp Ala Ala Leu Val

245 250 255

Val Leu Ser Gln Ala Leu Asn Gly Leu Leu Met Ser Ala Val Met Lys
260 265 270
His Gly Ser Ser Ile Thr Arg Leu Phe Val Val Ser Cys Ser Leu Val
275 280 285
Val Asn Ala Val Leu Ser Ala Val Leu Leu Arg Leu Gln Leu Thr Ala
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Ala Phe Phe Leu Ala Thr Leu Leu Ile Gly Leu Ala Met Arg Leu Tyr
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Tyr Gly Ser Arg

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Tyr Lys Thr Cys Arg Arg Pro Arg Pro Val Val Thr Thr Thr Thr Ser
35 40 45
Thr Thr Val Val His Ala Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro
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Ser Tyr Pro Gly Pro Ser Tyr Gln Gly Tyr His Thr Met Pro Pro Gln

65 70 75 80

Pro Gly Met Pro Ala Ala Pro Tyr Pro Met Gln Tyr Pro Pro Pro Tyr

85 90 95

Pro Ala Gln Pro Met Gly Pro Pro Ala Tyr His Glu Thr Leu Ala Gly

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Gly Ala Ala Ala Pro Tyr Pro Ala Ser Gln Pro Pro Tyr Asn Pro Ala

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Tyr Met Asp Ala Pro Lys Ala Ala Leu

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Phe Lys Val Ala Thr Pro Tyr Ser Leu Tyr Val Cys Pro Glu Gly Gln

35 40 45

Asn Val Thr Leu Thr Cys Arg Leu Leu Gly Pro Val Asp Lys Gly His

50 55 60

Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg Ser Ser Arg Gly Glu Val

65 70 75 80

Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg Asn Leu Thr Phe Gln Asp

85 90 95

Leu His Leu His His Gly Gly His Gln Ala Ala Asn Thr Ser His Asp

100 105 110

Leu Ala Gln Arg His Gly Leu Glu Ser Ala Ser Asp His His Gly Asn

115 120 125

Phe Ser Ile Thr Met Arg Asn Leu Thr Leu Leu Asp Ser Gly Leu Tyr

130 135 140

Cys Cys Leu Val Val Glu Ile Arg His His His Ser Glu His Arg Val

145 150 155 160

His Gly Ala Met Glu Leu Gln Val Gln Thr Gly Lys Asp Ala Pro Ser

165 170 175

Asn Cys Val Val Tyr Pro Ser Ser Ser Gln Glu Ser Glu Asn Ile Thr

180 185 190

Ala Ala Ala Leu Ala Thr Gly Ala Cys Ile Val Gly Ile Leu Cys Leu

195 200 205

Pro Leu Ile Leu Leu Leu Val Tyr Lys Gln Arg Gln Ala Ala Ser Asn

210 215 220

Arg Arg Ala Gln Glu Leu Val Arg Met Asp Ser Asn Ile Gln Gly Ile

225 230 235 240

Glu Asn Pro Gly Phe Glu Ala Ser Pro Pro Ala Gln Gly Ile Pro Glu

245 250 255

Ala Lys Val Arg His Pro Leu Ser Tyr Val Ala Gln Arg Gln Pro Ser

260 265 270

Glu Ser Gly Arg His Leu Leu Ser Glu Pro Ser Thr Pro Leu Ser Pro
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Leu Asn Ser Phe Gly Phe Tyr Thr Asn Gly Ser Leu Glu Val Glu Leu
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Ser Val Leu Arg Leu Gly Leu Arg Glu Ala Glu Glu Lys Ser Leu Leu
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Val Gly Phe Ser Leu Ser Arg Val Arg Ser Gly Arg Val Arg Ser Tyr
85 90 95

Ser Thr Arg Asp Phe Gln Asp Cys Pro Leu Gln Lys Asn Ser Ser Ser
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Phe Leu Val Leu Phe Leu Ile Asn Thr Lys Asp Leu Gln Val Gln Val
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Arg Lys Tyr Gly Glu Gln Lys Thr Leu Phe Ile Phe Pro Gly Leu Leu
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Pro Glu Ala Pro Ser Lys Pro Gly Leu Pro Lys Pro Gln Ala Thr Val
145 150 155 160
Pro Arg Lys Val Asp Gly Gly Gly Thr Ser Ala Ala Ser Lys Pro Lys
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Ser Thr Pro Ala Val Ile Gln Gly Pro Ser Gly Lys Asp Lys Asp Leu
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Val Leu Gly Leu Ser His Leu Asn Asn Ser Tyr Asn Phe Ser Phe His
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Val Val Ile Gly Ser Gln Ala Glu Glu Gly Gln Tyr Ser Leu Asn Phe
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His Asn Cys Asn Asn Ser Val Pro Gly Lys Glu His Pro Phe Asp Ile
225 230 235 240
Thr Val Met Ile Arg Glu Lys Asn Pro Asp Gly Phe Leu Ser Ala Ala
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Glu Met Pro Leu Phe Lys Leu Tyr Met Val Met Ser Ala Cys Phe Leu
260 265 270
Ala Ala Gly Ile Phe Trp Val Ser Ile Leu Cys Arg Asn Thr Tyr Ser
275 280 285
Val Phe Lys Ile His Trp Leu Met Ala Ala Leu Ala Phe Thr Lys Ser

290 295 300

Ile Ser Leu Leu Phe His Ser Ile Asn Tyr Tyr Phe Ile Asn Ser Gln

305 310 315 320

Gly His Pro Ile Glu Gly Leu Ala Val Met Tyr Tyr Ile Ala His Leu

325 330 335

Leu Lys Gly Ala Leu Leu Phe Ile Thr Ile Ala Leu Ile Gly Ser Gly

340 345 350

Trp Ala Phe Ile Lys Tyr Val Leu Ser Asp Lys Glu Lys Lys Val Phe

355 360 365

Gly Ile Val Ile Pro Met Gln Val Leu Ala Asn Val Ala Tyr Ile Ile

370 375 380

Ile Glu Ser Arg Glu Glu Gly Ala Ser Asp Tyr Val Leu Trp Lys Glu

385 390 395 400

Ile Leu Phe Leu Val Asp Leu Ile Cys Cys Gly Ala Ile Leu Phe Pro

405 410 415

Val Val Trp Ser Ile Arg His Leu Gln Asp Ala Ser Gly Thr Asp Gly

420 425 430

Lys Val Ala Val Asn Leu Ala Lys Leu Lys Leu Phe Arg His Tyr Tyr

435 440 445

Val Met Val Ile Cys Tyr Val Tyr Phe Thr Arg Ile Ile Ala Ile Leu

450 455 460

Leu Gln Val Ala Val Pro Phe Gln Trp Gln Trp Leu Tyr Gln Leu Leu

465 470 475 480

Val Glu Gly Ser Thr Leu Ala Phe Phe Val Leu Thr Gly Tyr Lys Phe

485 490 495

Gln Pro Thr Gly Asn Asn Pro Tyr Leu Gln Leu Pro Gln Glu Asp Glu
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Glu Asp Val Gln Met Glu Gln Val Met Thr Asp Ser Gly Phe Arg Glu
515 520 525

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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Met Ser Pro

1

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Ser Pro Thr Ala Leu Phe Cys Leu Gly Leu Cys Leu Gly Arg Val Pro
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Ala Gln Ser Gly Pro Leu Pro Lys Pro Ser Leu Gln Ala Leu Pro Ser
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Ser Leu Val Pro Leu Glu Lys Pro Val Thr Leu Arg Cys Gln Gly Pro
40 45 50

ccg ggc gtg gac ctg tac cgc ctg gag aag ctg agt tcc agc agg tac 246
Pro Gly Val Asp Leu Tyr Arg Leu Glu Lys Leu Ser Ser Ser Arg Tyr
55 60 65

cag gat cag gca gtc ctc ttc atc ccg gcc atg aag aga agt ctg gct 294
Gln Asp Gln Ala Val Leu Phe Ile Pro Ala Met Lys Arg Ser Leu Ala
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gga cgc tac cgc tgc tcc tac cag aac gga agc ctc tgg tcc ctg ccc 342
Gly Arg Tyr Arg Cys Ser Tyr Gln Asn Gly Ser Leu Trp Ser Leu Pro
85 90 95

agc gac cag ctg gag ctc gtt gcc acg gga gtt ttt gcc aaa ccc tcg 390
Ser Asp Gln Leu Glu Leu Val Ala Thr Gly Val Phe Ala Lys Pro Ser
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Leu Ser Ala Gln Pro Gly Pro Ala Val Ser Ser Gly Gly Asp Val Thr
120 125 130

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Leu Gln Cys Gln Thr Arg Tyr Gly Phe Asp Gln Phe Ala Leu Tyr Lys
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Glu Gly Asp Pro Ala Pro Tyr Lys Asn Pro Glu Arg Trp Tyr Arg Ala
150 155 160

agt ttt ccc atc atc acg gtg acc gcc gcc cac agc gga acc tac cga 582
Ser Phe Pro Ile Ile Thr Val Thr Ala Ala His Ser Gly Thr Tyr Arg
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Cys Tyr Ser Phe Ser Ser Arg Asp Pro Tyr Leu Trp Ser Ala Pro Ser
180 185 190 195

gac ccc ctg gag ctt gtg gtc aca gga acc tct gtg acc ccc agc cgg 678
Asp Pro Leu Glu Leu Val Val Thr Gly Thr Ser Val Thr Pro Ser Arg
200 205 210

tta cca aca gaa cca cct tcc tcg gta gca gaa ttc tca gaa gcc acc 726
Leu Pro Thr Glu Pro Pro Ser Ser Val Ala Glu Phe Ser Glu Ala Thr
215 220 225

gct gaa ctg acc gtc tca ttc aca aac gaa gtc ttc aca act gag act 774
Ala Glu Leu Thr Val Ser Phe Thr Asn Glu Val Phe Thr Thr Glu Thr
230 235 240

tct agg agt atc acc gcc agt cca aag gag tca gac tct cca gct ggt 822
Ser Arg Ser Ile Thr Ala Ser Pro Lys Glu Ser Asp Ser Pro Ala Gly
245 250 255

cct gcc cgc cag tac tac acc aag ggc aac ctg gtc cgg ata tgc ctc 870
Pro Ala Arg Gln Tyr Tyr Thr Lys Gly Asn Leu Val Arg Ile Cys Leu

260 265 270 275

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Gly Ala Val Ile Leu Ile Ile Leu Ala Gly Phe Leu Ala Glu Asp Trp

280 285 290

cac agc cgg agg aag cgc ctg cgg cac agg ggc agg gct gtg cag agg 966
His Ser Arg Arg Lys Arg Leu Arg His Arg Gly Arg Ala Val Gln Arg

295 300 305

ccg ctt ccg ccc ctc ccg ccc ctc ccg ctg acc cgg aaa tca cac ggg 1014
Pro Leu Pro Pro Leu Pro Pro Leu Pro Leu Thr Arg Lys Ser His Gly

310 315 320

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Gly Gln Asp Gly Gly Arg Gln Asp Val His Ser Arg Gly Leu Cys Ser

325 330 335

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Met Ala Ser Ser Ala Glu Gly Asp Glu

1 5

ggg act gtg gtg gcg ctg gcg ggg gtt ctg cag tcg ggt ttc cag gag 159

Gly Thr Val Val Ala Leu Ala Gly Val Leu Gln Ser Gly Phe Gln Glu

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ctg agc ctt aac aag ttg gcg acg tcc ctg ggc gcg tca gaa cag gcg 207

Leu Ser Leu Asn Lys Leu Ala Thr Ser Leu Gly Ala Ser Glu Gln Ala

30 35 40

ctg cgg ctg atc atc tcc atc ttc ctg ggt tac ccc ttt gct ttg ttt 255
Leu Arg Leu Ile Ile Ser Ile Phe Leu Gly Tyr Pro Phe Ala Leu Phe
45 50 55

tat cgg cat tac ctt ttc tac aag gag acc tac ctc atc cac ctc ttc 303
Tyr Arg His Tyr Leu Phe Tyr Lys Glu Thr Tyr Leu Ile His Leu Phe
60 65 70

cat acc ttt aca ggc ctc tca att gct tat ttt aac ttt gga aac cag 351
His Thr Phe Thr Gly Leu Ser Ile Ala Tyr Phe Asn Phe Gly Asn Gln
75 80 85

ctc tac cac tcc ctg ctg tgt att gtg ctt cag ttc ctc atc ctt cga 399
Leu Tyr His Ser Leu Leu Cys Ile Val Leu Gln Phe Leu Ile Leu Arg
90 95 100 105

cta atg ggc cgc acc atc act gcc gtc ctc act acc ttt tgc ttc cag 447
Leu Met Gly Arg Thr Ile Thr Ala Val Leu Thr Thr Phe Cys Phe Gln
110 115 120

atg gcc tac ctt ctg gct gga tac tat tac act gcc acc ggc aac tac 495
Met Ala Tyr Leu Leu Ala Gly Tyr Tyr Tyr Thr Ala Thr Gly Asn Tyr
125 130 135

gat atc aag tgg aca atg cca cat tgt gtt ctg act ttg aag ctg att 543
Asp Ile Lys Trp Thr Met Pro His Cys Val Leu Thr Leu Lys Leu Ile
140 145 150

ggt ttg gct gtt gac tac ttt gac gga ggg aaa gat cag aat tcc ttg 591
Gly Leu Ala Val Asp Tyr Phe Asp Gly Gly Lys Asp Gln Asn Ser Leu
155 160 165

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Ser Ser Glu Gln Gln Lys Tyr Ala Ile Arg Gly Val Pro Ser Leu Leu
170 175 180 185

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Glu Val Ala Gly Phe Ser Tyr Phe Tyr Gly Ala Phe Leu Val Gly Pro
190 195 200

cag ttc tca atg aat cac tac atg aag ctg gtg cag gga gag ctg att 735
Gln Phe Ser Met Asn His Tyr Met Lys Leu Val Gln Gly Glu Leu Ile
205 210 215

gac ata cca gga aag ata cca aac agc atc att cct gct ctc aag cgc 783
Asp Ile Pro Gly Lys Ile Pro Asn Ser Ile Ile Pro Ala Leu Lys Arg
220 225 230

ctg agt ctg ggc ctt ttc tac cta gtg ggc tac aca ctg ctc agc ccc 831
Leu Ser Leu Gly Leu Phe Tyr Leu Val Gly Tyr Thr Leu Leu Ser Pro
235 240 245

cac atc aca gaa gac tat ctc ctc act gaa gac tat gac aac cac ccc 879
His Ile Thr Glu Asp Tyr Leu Leu Thr Glu Asp Tyr Asp Asn His Pro
250 255 260 265

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Phe Trp Phe Arg Cys Met Tyr Met Leu Ile Trp Gly Lys Phe Val Leu
270 275 280

tac aaa tat gtc acc tgt tgg ctg gtc aca gaa gga gta tgc att ttg 975
Tyr Lys Tyr Val Thr Cys Trp Leu Val Thr Glu Gly Val Cys Ile Leu
285 290 295

acg ggc ctg ggc ttc aat ggc ttt gaa gaa aag ggc aag gca aag tgg 1023
Thr Gly Leu Gly Phe Asn Gly Phe Glu Glu Lys Gly Lys Ala Lys Trp

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ttc act ggc acc att gcc tca ttc aac atc aac acc aac gcc tgg gtg     1119
Phe Thr Gly Thr Ile Ala Ser Phe Asn Ile Asn Thr Asn Ala Trp Val
330                 335                 340                 345
gcc cgc tac atc ttc aaa cga ctc aag ttc ctt gga aat aaa gaa ctc     1167
Ala Arg Tyr Ile Phe Lys Arg Leu Lys Phe Leu Gly Asn Lys Glu Leu
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tct cag ggt ctc tcg ttg cta ttc ctg gcc ctc tgg cac ggc ctg cac     1215
Ser Gln Gly Leu Ser Leu Leu Phe Leu Ala Leu Trp His Gly Leu His
            365                 370                 375
tca gga tac ctg gtc tgc ttc cag atg gaa ttc ctc att gtt att gtg     1263
Ser Gly Tyr Leu Val Cys Phe Gln Met Glu Phe Leu Ile Val Ile Val
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gaa aga cag gct gcc agg ctc att caa gag agc ccc acc ctg agc aag     1311
Glu Arg Gln Ala Ala Arg Leu Ile Gln Glu Ser Pro Thr Leu Ser Lys
    395                 400                 405
ctg gcc gcc att act gtc ctc cag ccc ttc tac tat ttg gtg caa cag     1359
Leu Ala Ala Ile Thr Val Leu Gln Pro Phe Tyr Tyr Leu Val Gln Gln
410                 415                 420                 425
acc atc cac tgg ctc ttc atg ggt tac tcc atg act gcc ttc tgc ctc     1407
Thr Ile His Trp Leu Phe Met Gly Tyr Ser Met Thr Ala Phe Cys Leu
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Phe Thr Trp Asp Lys Trp Leu Lys Val Tyr Lys Ser Ile Tyr Phe Leu
445 450 455

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Gly His Ile Phe Phe Leu Ser Leu Leu Phe Ile Leu Pro Tyr Ile His
460 465 470

aaa gca atg gtg cca agg aaa gag aag tta aag aag atg gaa taatc 1550
Lys Ala Met Val Pro Arg Lys Glu Lys Leu Lys Lys Met Glu
475 480 485

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<213> Homo sapiens

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Gly Ala Thr Arg Leu Leu Leu Leu Leu Met Ala Val Ala Ala Pro
10 15 20

agt cga gcc cgg ggc agc ggc tgc cgg gcc ggg act ggt gcg cga ggg 148
Ser Arg Ala Arg Gly Ser Gly Cys Arg Ala Gly Thr Gly Ala Arg Gly
25 30 35

gct ggg gcg gaa ggt cga gag ggc gag gcc tgt ggc acg gtg ggg ctg 196
Ala Gly Ala Glu Gly Arg Glu Gly Glu Ala Cys Gly Thr Val Gly Leu
40 45 50

ctg ctg gag cac tca ttt gag atc gat gac agt gcc aac ttc cgg aag 244
Leu Leu Glu His Ser Phe Glu Ile Asp Asp Ser Ala Asn Phe Arg Lys
55 60 65 70

cgg ggc tca ctg ctc tgg aac cag cag gat ggt acc ttg tcc ctg tca 292
Arg Gly Ser Leu Leu Trp Asn Gln Gln Asp Gly Thr Leu Ser Leu Ser
75 80 85

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Gln Arg Gln Leu Ser Glu Glu Glu Arg Gly Arg Leu Arg Asp Val Ala
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gcc ctg aat ggc ctg tac cgg gtc cgg atc cca agg cga ccc ggg gcc 388
Ala Leu Asn Gly Leu Tyr Arg Val Arg Ile Pro Arg Arg Pro Gly Ala
105 110 115

ctg gat ggc ctg gaa gct ggt ggc tat gtc tcc tcc ttt gtc cct gcg 436
Leu Asp Gly Leu Glu Ala Gly Gly Tyr Val Ser Ser Phe Val Pro Ala
120 125 130

tgc tcc ctg gtg gag tcg cac ctg tcg gac cag ctg acc ctg cac gtg 484
Cys Ser Leu Val Glu Ser His Leu Ser Asp Gln Leu Thr Leu His Val
135 140 145 150

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Asp Val Ala Gly Asn Val Val Gly Val Ser Val Val Thr His Pro Gly
155 160 165

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Gly Cys Arg Gly His Glu Val Glu Asp Val Asp Leu Glu Leu Phe Asn
170 175 180

acc tcg gtg cag ctg cag ccg ccc acc aca gcc cca ggc cct gag acg 628
Thr Ser Val Gln Leu Gln Pro Pro Thr Thr Ala Pro Gly Pro Glu Thr
185 190 195

gcg gcc ttc att gag cgc ctg gag atg gaa cag gcc cag aag gcc aag 676
Ala Ala Phe Ile Glu Arg Leu Glu Met Glu Gln Ala Gln Lys Ala Lys
200 205 210

aac ccc cag gag cag aag tcc ttc ttc gcc aaa tac tgg atg tac atc 724

Asn Pro Gln Glu Gln Lys Ser Phe Phe Ala Lys Tyr Trp Met Tyr Ile

215 220 225 230

att ccc gtc gtc ctg ttc ctc atg atg tca gga gcg cca gac acc ggg 772

Ile Pro Val Val Leu Phe Leu Met Met Ser Gly Ala Pro Asp Thr Gly

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Gly Gln Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly Arg

250 255 260

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Leu Leu Asp Pro Ala Glu Gly Leu Ser Arg Arg Lys Lys Thr Ser Leu

15 20 25

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Trp Phe Val Gly Ser Leu Leu Leu Val Ser Val Leu Ile Val Thr Val

30 35 40

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Gly Leu Ala Ala Thr Thr Arg Thr Glu Asn Val Thr Val Gly Gly Tyr

45 50 55

tac cca ggg atc att ctc ggc ttt gga tct ttc tta gga att att ggc 241
Tyr Pro Gly Ile Ile Leu Gly Phe Gly Ser Phe Leu Gly Ile Ile Gly
60 65 70

atc aac ttg gtg gag aat aga agg caa atg ctg gtg gca gcg atc gtg 289
Ile Asn Leu Val Glu Asn Arg Arg Gln Met Leu Val Ala Ala Ile Val
75 80 85 90

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Phe Ile Ser Phe Gly Val Val Ala Ala Phe Cys Cys Ala Ile Val Asp
95 100 105

ggc gta ttt gca gca cag cac att gaa ccg agg ccc ctc acc acg gga 385
Gly Val Phe Ala Ala Gln His Ile Glu Pro Arg Pro Leu Thr Thr Gly
110 115 120

aga tgc cag ttt tac tcc agt ggg gtg ggg tac ttg tac gat gtc tac 433
Arg Cys Gln Phe Tyr Ser Ser Gly Val Gly Tyr Leu Tyr Asp Val Tyr
125 130 135

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Gln Thr Glu Val Ser Arg Ser Thr Glu Ile His Val Gly Phe Ala Gln
140 145 150

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Leu Thr Pro Pro Thr Pro Arg Gly Phe Pro Cys Thr
155 160 165

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Arg Gln Arg Arg Pro Leu Arg Pro Gln Val Val Thr Asp Asp Asp Gly
10 15 20

cag gcc ccg gag gct aag gac ggc agc tcc ttt agc ggc aga gtt ttc 148
Gln Ala Pro Glu Ala Lys Asp Gly Ser Ser Phe Ser Gly Arg Val Phe
25 30 35

cga gtg acc ttc ttg atg ctg gct gtt tct ctc acc gtt ccc ctg ctt 196
Arg Val Thr Phe Leu Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu
40 45 50 55

gga gcc atg atg ctg ctg gaa tct cct ata gat cca cag cct ctc agc 244
Gly Ala Met Met Leu Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser
60 65 70

ttc aaa gaa ccc ccg ctc ttg ctt ggt gtt ctg cat cca aat acg aag 292
Phe Lys Glu Pro Pro Leu Leu Leu Gly Val Leu His Pro Asn Thr Lys
75 80 85

ctg cga cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag 340
Leu Arg Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu
90 95 100

tcc ata gca cat att ggg gat gtg atg ttt act ggg aca gca gat ggc 388
Ser Ile Ala His Ile Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly

105 110 115

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Arg Val Val Lys Leu Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe
120 125 130 135

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Gly Ser Gly Pro Cys Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg
140 145 150

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Pro Leu Gly Ile Arg Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp
155 160 165

gca tac aag gga cta ttt gaa gta aat ccc tgg aaa cgt gaa gtg aaa 580
Ala Tyr Lys Gly Leu Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys
170 175 180

ctg ctg ctg tcc tcc gag aca ccc att gag ggg aag aac atg tcc ttt 628
Leu Leu Leu Ser Ser Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe
185 190 195

gtg aat gat ctt aca gtc act cag gat ggg agg aag att tat ttc acc 676
Val Asn Asp Leu Thr Val Thr Gln Asp Gly Arg Lys Ile Tyr Phe Thr
200 205 210 215

gat tct agc agc aaa tgg caa aga cga gac tac ctg ctt ctg gtg atg 724
Asp Ser Ser Ser Lys Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met
220 225 230

gag ggc aca gat gac ggg cgc ctg ctg gag tat gat act gtg acc agg 772
Glu Gly Thr Asp Asp Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg
235 240 245

gaa gta aaa gtt tta ttg gac cag ctg cgg ttc ccg aat gga gtc cag 820
Glu Val Lys Val Leu Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln
250 255 260

ctg tct cct gca gaa gac ttt gtc ctg gtg gca gaa aca acc atg gcc 868
Leu Ser Pro Ala Glu Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala
265 270 275

agg ata cga aga gtc tac gtt tct ggc ctg atg aag ggc ggg gct gat 916
Arg Ile Arg Arg Val Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp
280 285 290 295

ctg ttt gtg gag aac atg cct gga ttt cca gac aac atc cgg ccc agc 964
Leu Phe Val Glu Asn Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser
300 305 310

agc tct ggg ggg tac tgg gtg ggc atg tcg acc atc cgc cct aac cct 1012
Ser Ser Gly Gly Tyr Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro
315 320 325

ggg ttt tcc atg ctg gat ttc tta tct gag aga ccc tgg att aaa agg 1060
Gly Phe Ser Met Leu Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg
330 335 340

atg att ttt aag ctc ttt agt caa gag acg gtg atg aag ttt gtg ccg 1108
Met Ile Phe Lys Leu Phe Ser Gln Glu Thr Val Met Lys Phe Val Pro
345 350 355

cgg tac agc ctc gtc cta gaa ctc agc gac agc ggt gcc ttc cgg aga 1156
Arg Tyr Ser Leu Val Leu Glu Leu Ser Asp Ser Gly Ala Phe Arg Arg
360 365 370 375

agc ctg cat gat ccc gat ggg ctg gtg gcc acc tac atc agc gag gtg 1204

Ser Leu His Asp Pro Asp Gly Leu Val Ala Thr Tyr Ile Ser Glu Val
380 385 390

cac gaa cac gat ggg cac ctg tac ctg ggc tct ttc agg tcc ccc ttc 1252
His Glu His Asp Gly His Leu Tyr Leu Gly Ser Phe Arg Ser Pro Phe
395 400 405

ctc tgc aga ctc agc ctc cag gct gtt tagccctccc agatagctgc c 1300
Leu Cys Arg Leu Ser Leu Gln Ala Val
410 415

cctgccacgc aggccaggag tcttcacact caggcaccag gcctggtcca ggaggagctg 1360

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ctg ctg ctg ctg gga gcc tgg gcc atc cca ggg ggc ctc ggg gac agg 99
Leu Leu Leu Leu Gly Ala Trp Ala Ile Pro Gly Gly Leu Gly Asp Arg
10 15 20

gcg cca ctc aca gcc aca gcc cca caa ctg gat gat gag gag atg tac 147
Ala Pro Leu Thr Ala Thr Ala Pro Gln Leu Asp Asp Glu Glu Met Tyr
25 30 35 40

tca gcc cac atg ccc gct cac ctg cgc tgt gat gcc tgc aga gct gtg 195
Ser Ala His Met Pro Ala His Leu Arg Cys Asp Ala Cys Arg Ala Val
45 50 55

gct tac cag gtg agt cct tca cca ctg tca ccc tgc cct gct cac acc 243
Ala Tyr Gln Val Ser Pro Ser Pro Leu Ser Pro Cys Pro Ala His Thr
60 65 70

cct tct caa gcc aga ccc ctc cac cca cct cac att cca cca ccg gcc 291

Pro Ser Gln Ala Arg Pro Leu His Pro Pro His Ile Pro Pro Pro Ala

75 80 85

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Phe Asp Pro Gln Ser Leu Pro Leu Gly Ile Lys Pro Gln Met Gln Pro

90 95 100

ttc ata tat tcc atg cct cag ttt acc cat ctg cct gcc ta 380

Phe Ile Tyr Ser Met Pro Gln Phe Thr His Leu Pro Ala

105 110 115

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tccttagact tctcccttte caggcccatc cttgagtccg gactccctcc ccaaccctga 500

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<213> Homo sapiens

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gtattctctc tggcaatgtt ccacggcttc tccttcctgg gagctggctc cataacttga 180

ttttccccaa acgtgttgca atcccctgctg ccccttagcc acccagggtc ttgtgtgggt 240

atg agt gta gag gat ggg ggt atg cca ggc ctg ggc cgt ccc agg cag 288
Met Ser Val Glu Asp Gly Gly Met Pro Gly Leu Gly Arg Pro Arg Gln
1 5 10 15

gcc cgc tgg acc ctg atg cta ctc cta tcc act gcc atg tac ggt gcc 336
Ala Arg Trp Thr Leu Met Leu Leu Leu Ser Thr Ala Met Tyr Gly Ala
20 25 30

cat gcc cca ttg ctg gca ctg tgc cat gtg gac ggc cga gtg ccc ttc 384
His Ala Pro Leu Leu Ala Leu Cys His Val Asp Gly Arg Val Pro Phe
35 40 45

cgg ccc tcc tca gcc gtg ctg ctg act gag ctg acc aag cta ctg tta 432
Arg Pro Ser Ser Ala Val Leu Leu Thr Glu Leu Thr Lys Leu Leu Leu
50 55 60

tgc gcc ttc tcc ctt ctg gta ggc tgg caa gca tgg ccc cag ggg ccc 480
Cys Ala Phe Ser Leu Leu Val Gly Trp Gln Ala Trp Pro Gln Gly Pro
65 70 75 80

cca ccc tgg cgc cag gct gct ccc ttc gca cta tca gcc ctg ctc tat 528
Pro Pro Trp Arg Gln Ala Ala Pro Phe Ala Leu Ser Ala Leu Leu Tyr
85 90 95

ggc gct aac aac aac ctg gtg atc tat ctt cag cgt tac atg gac ccc 576
Gly Ala Asn Asn Asn Leu Val Ile Tyr Leu Gln Arg Tyr Met Asp Pro
100 105 110

agc acc tac cag gtg ctg agt aat ctc aag att gga agc aca gct gtg 624
Ser Thr Tyr Gln Val Leu Ser Asn Leu Lys Ile Gly Ser Thr Ala Val
115 120 125

ctc tac tgc ctc tgc ctc cgg cac cgc ctc tct gtg cgt cag ggg tta 672

Leu Tyr Cys Leu Cys Leu Arg His Arg Leu Ser Val Arg Gln Gly Leu
130 135 140

gcg ctg ctg ctg ctg atg gct gcg gga gcc tgc tat gca gca ggg ggc 720
Ala Leu Leu Leu Leu Met Ala Ala Gly Ala Cys Tyr Ala Ala Gly Gly
145 150 155 160

ctt caa gtt ccc ggg aac acc ctt ccc agt ccc cct cca gca gct gct 768
Leu Gln Val Pro Gly Asn Thr Leu Pro Ser Pro Pro Pro Ala Ala Ala
165 170 175

gcc agc ccc atg ccc ctg cat atc act ccg cta ggc ctg ctg ctc ctc 816
Ala Ser Pro Met Pro Leu His Ile Thr Pro Leu Gly Leu Leu Leu Leu
180 185 190

att ctg tac tgc ctc atc tca ggc ttg tcg tca gtg tac aca gag ctg 864
Ile Leu Tyr Cys Leu Ile Ser Gly Leu Ser Ser Val Tyr Thr Glu Leu
195 200 205

ctc atg aag cga cag cgg ctg ccc ctg gca ctt cag aac ctc ttc ctc 912
Leu Met Lys Arg Gln Arg Leu Pro Leu Ala Leu Gln Asn Leu Phe Leu
210 215 220

tac act ttt ggt gtg ctt ctg aat cta ggt ctg cat gct ggc ggc ggc 960
Tyr Thr Phe Gly Val Leu Leu Asn Leu Gly Leu His Ala Gly Gly Gly
225 230 235 240

tct ggc cca ggc ctc ctg gaa ggt ttc tca gga tgg gca gca ctc gtg 1008
Ser Gly Pro Gly Leu Leu Glu Gly Phe Ser Gly Trp Ala Ala Leu Val
245 250 255

gtg ctg agc cag gca cta aat gga ctg ctc atg tct gct gtc atg aag 1056
Val Leu Ser Gln Ala Leu Asn Gly Leu Leu Met Ser Ala Val Met Lys

260 265 270

cat ggc agc agc atc aca cgc ctc ttt gtg gtg tcc tgc tcg ctg gtg 1104
His Gly Ser Ser Ile Thr Arg Leu Phe Val Val Ser Cys Ser Leu Val
275 280 285

gtc aac gcc gtg ctc tca gca gtc ctg cta cgg ctg cag ctc aca gcc 1152
Val Asn Ala Val Leu Ser Ala Val Leu Leu Arg Leu Gln Leu Thr Ala
290 295 300

gcc ttc ttc ctg gcc aca ttg ctc att ggc ctg gcc atg cgc ctg tac 1200
Ala Phe Phe Leu Ala Thr Leu Leu Ile Gly Leu Ala Met Arg Leu Tyr
305 310 315 320

tat ggc agc cgc tagtccctga caacttccac cctgattccg gaccctgt 1250
Tyr Gly Ser Arg

agattgggcg ccaccaccag atccccctcc caggccttcc tccctctccc atcagcagcc 1310
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tcagtgtctc tttaactgca taagcaataa gatcttaata aagtcttcta ggctgtaggg 2150

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<211> 1738

<212> DNA

<213> Homo sapiens

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<221> CDS

<222> (95)...(508)

<400> 28

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Met Gly Phe Gly Ala Thr

1 5

ttg gcc gtt ggc ctg acc atc ttt gtg ctg tct gtc gtc act atc atc 160

Leu Ala Val Gly Leu Thr Ile Phe Val Leu Ser Val Val Thr Ile Ile

10 15 20

atc tgc ttc acc tgc tcc tgc tgc tgc ctt tac aag acg tgc cgc cga 208

Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Thr Cys Arg Arg

25 30 35

cca cgt ccg gtt gtc acc acc acc aca tcc acc act gtg gtg cat gcc 256
Pro Arg Pro Val Val Thr Thr Thr Ser Thr Thr Val Val His Ala
40 45 50

cct tat cct cag cct cca agt gtg ccg ccc agc tac cct gga cca agc 304
Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro Ser Tyr Pro Gly Pro Ser
55 60 65 70

tac cag ggc tac cac acc atg ccg cct cag cca ggg atg cca gca gca 352
Tyr Gln Gly Tyr His Thr Met Pro Pro Gln Pro Gly Met Pro Ala Ala
75 80 85

ccc tac cca atg cag tac cca cca cct tac cca gcc cag ccc atg ggc 400
Pro Tyr Pro Met Gln Tyr Pro Pro Pro Tyr Pro Ala Gln Pro Met Gly
90 95 100

cca ccg gcc tac cac gag acc ctg gct gga gga gca gcc gcg ccc tac 448
Pro Pro Ala Tyr His Glu Thr Leu Ala Gly Gly Ala Ala Ala Pro Tyr
105 110 115

ccc gcc agc cag cct cct tac aac ccg gcc tac atg gat gcc ccg aag 496
Pro Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Ala Pro Lys
120 125 130

gcg gcc ctc tgagcattcc ctggcctctc tggctgccac ttggttatgt tgtgt 550
Ala Ala Leu
135

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<212> DNA

<213> Homo sapiens

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ctctgcgcgt ccgacggcga c atg ggc gtc ccc acg gcc ctg gag gcc ggc 111
Met Gly Val Pro Thr Ala Leu Glu Ala Gly
1 5 10

agc tgg cgc tgg gga tcc ctg ctc ttc gct ctc ttc ctg gct gcg tcc 159
Ser Trp Arg Trp Gly Ser Leu Leu Phe Ala Leu Phe Leu Ala Ala Ser
15 20 25

cta ggt ccg gtg gca gcc ttc aag gtc gcc acg ccg tat tcc ctg tat 207
Leu Gly Pro Val Ala Ala Phe Lys Val Ala Thr Pro Tyr Ser Leu Tyr
30 35 40

gtc tgt ccc gag ggg cag aac gtc acc ctc acc tgc agg ctc ttg ggc 255
Val Cys Pro Glu Gly Gln Asn Val Thr Leu Thr Cys Arg Leu Leu Gly
45 50 55

cct gtg gac aaa ggg cac gat gtg acc ttc tac aag acg tgg tac cgc 303
Pro Val Asp Lys Gly His Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg
60 65 70

agc tcg agg ggc gag gtg cag acc tgc tca gag cgc cgg ccc atc cgc 351
Ser Ser Arg Gly Glu Val Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg
75 80 85 90

aac ctc acg ttc cag gac ctt cac ctg cac cat gga ggc cac cag gct 399
Asn Leu Thr Phe Gln Asp Leu His Leu His His Gly Gly His Gln Ala
95 100 105

gcc aac acc agc cac gac ctg gct cag cgc cac ggg ctg gag tcg gcc 447

Ala Asn Thr Ser His Asp Leu Ala Gln Arg His Gly Leu Glu Ser Ala
110 115 120

tcc gac cac cat ggc aac ttc tcc atc acc atg cgc aac ctg acc ctg 495
Ser Asp His His Gly Asn Phe Ser Ile Thr Met Arg Asn Leu Thr Leu
125 130 135

ctg gat agc ggc ctc tac tgc tgc ctg gtg gtg gag atc agg cac cac 543
Leu Asp Ser Gly Leu Tyr Cys Cys Leu Val Val Glu Ile Arg His His
140 145 150

cac tcg gag cac agg gtc cat ggt gcc atg gaa ctg cag gtg cag aca 591
His Ser Glu His Arg Val His Gly Ala Met Glu Leu Gln Val Gln Thr
155 160 165 170

ggc aaa gat gca cca tcc aac tgt gtg gtg tac cca tcc tcc tcc cag 639
Gly Lys Asp Ala Pro Ser Asn Cys Val Val Tyr Pro Ser Ser Ser Gln
175 180 185

gag agt gaa aac atc acg gct gca gcc ctg gct acg ggt gcc tgc atc 687
Glu Ser Glu Asn Ile Thr Ala Ala Ala Leu Ala Thr Gly Ala Cys Ile
190 195 200

gta gga atc ctc tgc ctc ccc ctc atc ctg ctc ctg gtc tac aag caa 735
Val Gly Ile Leu Cys Leu Pro Leu Ile Leu Leu Leu Val Tyr Lys Gln
205 210 215

agg cag gca gcc tcc aac cgc cgt gcc cag gag ctg gtg cgg atg gac 783
Arg Gln Ala Ala Ser Asn Arg Arg Ala Gln Glu Leu Val Arg Met Asp
220 225 230

agc aac att caa ggg att gaa aac ccc ggc ttt gaa gcc tca cca cct 831
Ser Asn Ile Gln Gly Ile Glu Asn Pro Gly Phe Glu Ala Ser Pro Pro

235 240 245 250

gcc cag ggg ata ccc gag gcc aaa gtc agg cac ccc ctg tcc tat gtg 879

Ala Gln Gly Ile Pro Glu Ala Lys Val Arg His Pro Leu Ser Tyr Val

255 260 265

gcc cag cgg cag cct tct gag tct ggg cgg cat ctg ctt tcg gag ccc 927

Ala Gln Arg Gln Pro Ser Glu Ser Gly Arg His Leu Leu Ser Glu Pro

270 275 280

agc acc ccc ctg tct cct cca ggc ccc gga gac gtc ttc ttc cca tcc 975

Ser Thr Pro Leu Ser Pro Pro Gly Pro Gly Asp Val Phe Phe Pro Ser

285 290 295

ctg gac cct gtc cct gac tct cca aac ttt gag gtc atc tagccc 1020

Leu Asp Pro Val Pro Asp Ser Pro Asn Phe Glu Val Ile

300 305 310

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ggctctgtga gtggcctctc cctcctgctc tgggctcaga tactgtgaca tcccagaagc 1140

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Atty Docket No.: GIN-6730CPUS #4

DECLARATION, PETITION AND POWER OF ATTORNEY FOR PATENT APPLICATION

(Check one):

☐ Declaration Submitted with Initial Filing

☒ Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

the specification of which (check one):

☐ is attached hereto.

OR

☒ was filed on **16 June 2000** as PCT International Application Number **PCT/JP00/03942** and filed as .

☐ and was amended by PCT Article 19 Amendment on _____ (if applicable),

☐ and was amended by PCT Article 34 Amendment on _____ (if applicable).

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

PRIORITY CLAIM

(Check one):

☐ no such applications have been filed.

☒ such applications have been filed as follows

1) FOREIGN PRIORITY CLAIM: I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (dd,mm,yyyy)	Priority Not Claimed	Certified Copy Attached	
				Yes	No
11/194359	JP	08 July 1999 (08.07.99)	☐	☐	☒
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

2) PROVISIONAL PRIORITY CLAIM: I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Provisional Application Number(s)	Filing Date (dd/mm/yyyy)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

3) U.S./PCT PRIORITY CLAIM: I hereby claim the benefit under Title 35, United States Code, §120 of any United States application or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (dd/mm/yyyy)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(39)

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Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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